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FÉDÉRATION EUROPÉENNE
D'ASSOCIATIONS ET D'INDUSTRIES
PHARMACEUTIQUES

AVENUE LOUISE 250 BOITE 91 - B-1050 BRUXELLES - BELGIQUE
TEL. +32-2 626 25 55 - FAX. +32-2 626 25 66 TVA BE.418.762.559

Ref.: JR.EA/51.114

Telefax
Fax-N°: 44 207 418 8400
Aan/To/A: Mr. I. Brown
Van/From/De: Dr. J. Reden
Datum/Date: 28/4/2000 N° Pag.: 5

Professor Rolf BASS
EMEA
7, Westferry Circus
Canary Wharf,
LONDON E14 4HB

April 27, 2000

Dear Rolf,

Re. : "ICH E11 Step 2 guideline"

We are pleased to enclose the EFPIA comments on above-mentioned guideline.

Yours sincerely,

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Dr. Jürgen REDEN
Manager
Scientific, Technical & Regulatory Affairs

Copy to : Professor A. HILDEBRANDT
Dr. B. VAN ZWIETEN-BOOT
Dr. A. SAINT-RAYMOND
Dr. L. BRASSART

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EFPIA COMMENTS ON THE ICH E11 STEP 2 GUIDELINE : "CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION"

GENERAL COMMENTS

EFPIA considers that the structure of the guideline is straightforward and the topics are easy to find and to consult. The topics presentation is well-balanced. The content is adequate to provide a guidance for those who develop products for paediatric patients, although not too detailed. It helps minimising the exposure in paediatric patients. It helps identifying the pre-clinical and clinical studies needed for registration.

EFPIA would like to address the following general comments on the ICH E11 Step 2 guideline :

- EFPIA considers that paediatric formulations may need to be developed. However, when adults comprise the major patient population such that paediatric data are not immediately available, the possibilities for expanding treatment use of the product in children should be explored.

- Extrapolation of non-clinical and clinical adult safety data to paediatrics would be easier if standard paediatric weights or skin surface areas were provided for each category.

- There is no specific mention in the document of studies in healthy paediatric subjects. Such studies are happening, both in response to regulatory authorities requesting restrictions that would make patient paediatric studies impractical, and in response to internal project teams wishing to ensure that the maximum paediatric data is obtained in the minimum time.

SPECIFIC COMMENTS

1. INTRODUCTION

1.4 General principles

We suggest adding the following statement at the end of this section : "Thus, at specified points during the development of a new medicinal product, it may be appropriate for companies to discuss with regulatory authorities the data needed to support paediatric labelling. This is particularly important when the product is likely to be commonly used in paediatric patients, for diseases predominantly or exclusively affecting paediatric patients, if the product would provide a meaningful therapeutic benefit to paediatric patients over existing treatments, the product exhibits a very novel mechanism of action, or the product is indicated for a very significant or life-threatening illness."

2 GUIDELINES

2.1 Issues when initiating a paediatric medicinal product development programme

Page 5, we propose to reword the first sentence as follows: "If the medicinal product is intended for pediatric use, this use should be substantiated by appropriate data. "

Page 6, § 1 : we suggest broadening the last sentence, or adding to it that "In particular any issues associated with the development and maturity of the CNS, kidney, liver or lungs should be addressed."

2.2 Paediatric formulations

Overall, this section is rather prescriptive and some "case by case" wording may be more appropriate. Whilst it may be necessary to have different formulations with different concentrations available to facilitate dosing and compliance in children, the need to develop a large number of formulations and/or concentrations is likely to deter rather than encourage the conduct of paediatric development programmes, and may even introduce a greater potential for prescribing and dosing errors.

2.3 Timing of studies

2.3.2. Medicinal products intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options

We suggest the following wording : "Research with a medicinal product that may potentially reverse ore improve a life-threatening condition, but also may have severe adverse effects may be done in patients suffering from the disease. However, the IRB should thoroughly review the protocol taking into account the terminal status of study participants. The illness of subject as a strong driver to take any risk in order to gain access to a potentially life-saving treatment should be carefully considered in the recruitment of those patients."

2.3.2. Medicinal products intended to treat other diseases and conditions

Page 8, sentence 5 : we suggest amending to "...and the submission of paediatric data would be expected in the application whenever practically possible."

2.4 Types of studies

Although the guideline requires proof of efficacy for medicinal products where extrapolation of adult data is impossible using pharmacokinetic modelling, for example medicinal products which exert their action topically such as inhaled corticosteroids, there is no reference to dose ranging studies in these instances. With regard to dose ranging of topical medicinal products, measures to avoid unnecessary clinical studies should be explored (e.g. study using a physicochemical model to evaluate drug distribution and reference to ratio of adult/paediatric dose levels for a similar medicinal product which has a paediatric indication).

The second paragraph suggests that the extrapolation of efficacy data from adults, in certain specific cases, may remove the need for efficacy studies : adequate information for paediatric use may be obtained from pharmacokinetic studies together with safety or other studies.

Page 9, § 2 : we suggest that this paragraph be amended to include reference to comparison of dose on mg/m^2 basis here as well as in Section 2.4.1. (see comments below).

With regard to comparison of doses, Section 2.4.1. makes it clear that "dosing recommendations for most medicinal products used in the paediatric population are usually based on mg/kg up to a maximum adult dose". It would therefore facilitate extrapolation of non-clinical and clinical adult safety data to paediatrics if standard paediatric weights or skin surface areas were provided for each of the age ranges categorised in Sections 2.5.1.-2.5.5. We could therefore compare effects in animals or humans in terms of exposure seen following doses of X mg/kg or X mg/m^2.

We recognise that there is likely to be a lot of variability in these weights or surface areas but would suggest that, in each case, it should be possible to define a lower level (e.g. 50 kg adult weight often used in non-clinical safety assessments). Since use of a lower body weight or surface area would allow the highest estimate of dose per mg or m^2 this would provide a more robust assessment of safety.

Nowadays liquid chromatography mass spectrometry (LCMS) would be the preferred choice of analytical assay by most pharmaceutical pharmacokinetic laboratories. Gas chromatography mass spectrometry (GCMS) is an older technique. We suggest not quoting any specific analytical technique here as whatever is quoted is likely to become outdated fairly rapidly. Suggest deleting specific examples of techniques from Section 2.4.1. first bullet, and amending to "...use of more sensitive analytical assays for parent drugs..."

2.4.1 Pharmacokinetics

We recommend that the word "bioequivalence" be changed to "relative bioavailability". Some useful and acceptable paediatric formulations may not achieve bioequivalence but if the relative bioavailability were known, useful recommendations could be included in labelling to guide dosing of paediatric formulation in children.

We suggest deleting the reference to "population pharmacokinetic" in the last major and first sub-bullet. A group of 5-8 children in a pharmacokinetic study cannot approximate a population. We suggest changing the second sub-bullet to "optimal sampling theory" (i.e. not population pharmacokinetic), although it should be noted (at the end of the section) that the utility of this approach assumes that chilren are like adults (which will obviously not always be true and is the reason for the study in the first place).

2.4.2 Efficacy

We suggest amending the fifth sentence to "Measurement of subjective symptoms such as pain requires different assessment instruments in patients of different ages because of different levels of comprehension and communication."

As the ICH E10 guideline is still a draft, we suggest deleted the reference to it.

2.4.3 Safety

Further clarification of whether the following statement : "In addition, the dynamic processes of growth and development ... to determine possible effects on skeletal, behavioural, cognitive, sexual and immune maturation and development." applies to all medicinal products, or guidance on which types of medicinal products are relevant, would be helpful.

2.5 Age classification of paediatric patients

Since any classification by age is arbitrary and a flexible approach is needed to assure that studies reflect current knowledge of paediatric pharmacology, this opportunity should be taken to harmonise the age range 16-18 to avoid the need for reanalysis for different regions e.g. tabulations of pooled data are repeated in order to reclassify the same 17 year old patient as either "adult" or "adolescent" depending on which regulatory agency the summary is required for. This harmonisation need not impact clinical trials at the protocol level since national differences in definition of "adolescence" and "legal consent" will persist; but harmonisation of the clinical database for global programmes at the time of marketing application preparation would be beneficial.

We also suggest use of "less than" symbols (i.e. <) in the list of categorisations instead of the reference to "completed days, months or years" as this has the potential to lead to confusion and error. The draft guideline should be amended to:

- Pre-term newborn infants
- Term newborn infants (0 to <28 days)
- Infants and toddlers (28 days to < 24 months)

- Children (2 years to < 12 years)
- Adolescents (12 years to < 16-18 years)

We strongly agree with the statement that "Dividing the paediatric population into too many small age groups might needlessly increase the number of patients required" so we suggest that it is made clear that this categorisation applies to the overall clinical programme population and does not restrict the selection of age ranges for individual studies.

2.5.4 Children (2-11 years)

The wording could imply that long-term growth and development studies are necessary prior to product licence application.

2.5.5 Adolescents

The first paragraph states that pregnancy testing is necessary for females aged 12 or older. We would prefer that pregnancy testing should be discretionary, i.e. for females who are or have been sexually active.

In paragraph 4, we suggest that the requirement for monitoring use of unprescribed medicinal products is not made mandatory.

Last sentence specifies that medicinal products may affect the pubertal growth spurt and may affect final height. It would be helpful if there was further discussion regarding the types of compounds this may be applicable to, a discussion of the difficulties in gathering such data during clinical trials and the effect of considerable variability in the population regarding end-points (i.e. onset of puberty and final heights).

2.6 Ethical issues in paediatric studies

It is rare for the first study in paediatrics to provide definitive efficacy data because there will be no information regarding exposure/response etc. in this population. Hence, by definition, this study will be exploratory and paediatrics may not be expected to derive any benefit from the study.

Points to be noted in enrolment of patients who have been enrolled in other trials should be given, e.g. recommended interval between enrolment in studies.

2.6.3 Consent

First §, third sentence : since the definition of "assent" is not given in the ICH E6 guideline, consideration should be given to including a definition of this term within this guideline.